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EXAMINER

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WASHINGTON, DC 20004

ART UNIT	PAPER NUMBER
1802	8

DATE MAILED: 10/27/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined . ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-57 are pending in the application.
   Of the above, claims 1-31, 34-39, 44-49, 52+53 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 32, 33, 40-43, 50, 51 and 54-57 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-57 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

15. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-21, 24, 38, 39 and 48, drawn to monoclonal antibodies, detectably labelled monoclonal antibodies, chimeric antibodies, pharmaceutical compositions, and assay methods, classified for example, in Classes 530, 424 and 435, subclasses (387.3, 388.23, 391.3), 85.8 and 7.2, respectively.

II. Claims 22 and 23, drawn to TNF polypeptides, classified in Class 530, subclass 350.

III. Claims 25-31 and 49, drawn to polynucleotides encoding antibodies, transformed hosts, transfected hosts, and processes for preparing antibodies by culturing transformed/transfected hosts, classified for example in Classes 536 and 435, subclasses 23.53 and (70.21, 240.2 and 252.3), respectively.

IV. Claims 32, 33, 40-47 and 50, 51 and 54-57, drawn to methods for treating an animal by administering a pharmaceutical composition containing an antibody, classified in Class 424, subclass 85.8.

V. Claims 34-37, 52 and 53, drawn to methods for removing TNF-alpha from a sample and treatment methods involving removal of TNF-alpha from a body fluid and returning said body fluid to an animal, classified for example, in Classes 530 and 424, subclasses 413 and 85.8.

The inventions are distinct, each from the other because of the following reasons:

The claims of Groups I-III are drawn to structurally and functionally distinct products which are made by different methods and have separate and distinct utilities and are deemed to be patentably distinct. Group I contains claims drawn to antibodies, detectably labelled antibodies, chimeric antibodies and pharmaceutical compositions. Group II contains claims drawn to TNF peptides. Group III contains claims drawn to polynucleotides encoding antibodies, and hosts transformed or transfected with said polynucleotides. The examination of these inventions requires separate and divergent searches in the U.S. patent shoes and in the scientific literature and requires the consideration of separate issues in determining patentability.

Groups I and III-V contain claims drawn to methods which differ in the method objectives, method steps and parameters and in the reagents used. Group I contains claims drawn to assay methods using antibodies. Group III contains claims drawn to processes for preparing antibodies by culturing hosts transformed or transfected with polynucleotides encoding antibodies. Group IV contains claims drawn to methods for treating animals by administering antibodies to said animals. Group V contains claims drawn to methods for removing TNF from a sample and to treatment methods involving removal of TNF from a biological fluid and returning said body fluid to an animal. These methods are clearly distinct.

Inventions I and (IV and V) are related as product and process of use. The inventions can be shown to be distinct if either or

both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the products as claimed can be used in other and materially different methods of use as evidenced by the separate and distinct methods of use claimed in Groups I, IV and V.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classifications and recognized divergent subject matter and because the searches required for the groups are not co-extensive, restriction for examination purposes as indicated is proper.

16. Upon the election of Group IV above, a further election of species is required as follows:

Claims 41 and 43 are generic to a plurality of disclosed patentably distinct species comprising methods of treating an animal having a pathology mediated by TNF wherein the pathology is selected from I) alcohol-induced hepatitis; II) chronic inflammatory pathology; III) a neurodegenerative disease; IV) a vascular inflammatory disease; V) a graft-versus-host pathology; VI) Kaisaki's pathology and VII) a malignant pathology. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. T h e

above species are distinct in that they relate to methods of use of anti-TNF monoclonal antibodies for treatment of distinct diseases which differ in the disease pathology and disease mechanisms.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

17. Upon the election of Species III above, a further election of species is required as follows:

Claims 44 and 45 are generic to a plurality of disclosed patentably distinct species comprising: AIDS dementia complex; a demyelinating disease; multiple sclerosis; acute transverse myelitis; an extrapyramidal disorder; a cerebellar disorder; a lesion of the corticospinal system; a disorder of the basal ganglia; a hyperkinetic movement disorder; Huntington's Chorea; senile chorea; a drug-induced movement disorder; a hypokinetic movement disorder; Parkinson's disease; progressive supranucleo palsy; a structural lesion of the cerebellum; a spinocerebellar degeneration; spinal ataxia; Friedreich's ataxia; a cerebellar

cortical degeneration; a multiple systems degeneration; ataxia telangiectasia; a mitochondrial multisystem disorder; a demyelinating core disorder; acute transverse myelitisa; a disorder of the motor unit; a neurogenic muscular atrophy; anterior horn cell degeneration; amyotrophic lateral sclerosis; infantile spinal muscular atrophy; juvenile spinal muscular atrophy; Alzheimer's disease; Down's syndrome; a diffuse Lewy body disease; senile demential of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; subacute sclerosing panencephalitis; Hallerrorden-Spatz disease; dementia pugilistica. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed.

The above species are distinct in that they relate to methods of use of anti-TNF monoclonal antibodies for treatment of distinct diseases which differ in the disease pathology and disease mechanisms.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

18. During a telephone conversation with Mr. Townsend on 9/27/93 a provisional election was made with traverse to prosecute the invention of Group IV, claims 32, 33, 40-47, 50, 51 and 54-57. In response to the election of species requirement set forth in

paragraph 16, above, Applicant further elected species II. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-31, 34-39, 44-48, 49, 52, 53 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to non-elected inventions.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

19. Updating of the status of all U.S. Patent applications referred to in the specification is required. It is noted that applications 07/853,606 and 07/670,827 are now abandoned.

20. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The title should reflect that the invention under examination in this application relates to the use of TNF-alpha-specific antibodies for therapy.

21. This application has been filed with informal drawings which

are acceptable for examination purposes.

22. Applicant is reminded of the proper content of an Abstract of the Disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains.

If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure.

If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement.

In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof.

If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following: (1) if a machine or apparatus, its organization and operation; (2) if an article, its method of making; (3) if a chemical compound, its identity and use; (4) if a mixture, its ingredients; (5) if a process, the steps. Extensive mechanical and design details of apparatus should not be given.

The purported merit of the antibodies of the invention for the treatment of the vast array of diseases contemplated in the abstract is not substantiated by evidence on the record.

23. Claims 32 is objected to as depending from a claim which is withdrawn from consideration. Amendment of the claim to incorporate the limitations of the withdrawn claim is recommended. Claim 33 is objected to as being in improper dependent form. Claim 33 is drawn to a method of use of a pharmaceutical composition according to claim 42. Claim 42 is drawn to a method. In a

conversation with Mr. Townsend on 9/27/93, Mr. Townsend indicated that the dependency of claim 33 from claim 42 is a typographical error and that claim 33 is intended to depend from claim 48. For the purpose of applying prior art in this examination, claim 33 has been considered as depending from claim 48.

24. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 32, 33, 50 and 51 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 32, 33, 44 and 45, respectively, of copending application Serial No. 07/943,852. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

25. Claims 40-43, and 54-57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 40 and 41 of copending application Serial No. 07/943,852. Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept of administering anti-TNF antibodies for treating various pathologies. Certain of the pathologies treated by the copending claims are identical to those treated by the instant claims. The specific dosages recited in claims 56 and 57 are obvious over the copending claims.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been

patented.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

26. Claims 32, 33, 40-43, 50, 51 and 54-57 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32, 40, 41, 50, 54 and 56 are indefinite, to the extent that they depend from claim 24 which depends from claim 1, in the recitation of a "high-affinity" mouse monoclonal antibody because the phrase does not have a defined meaning in the art and the exact values of affinity constants considered to be "high-affinity" antibodies are not known. Thus, one of skill in the art could not determine the meets and bounds of the claimed subject matter. The specification provides does not define these phrases. Moreover, the specification is not enabling for antibodies having infinitely high affinity. The specification discloses only antibodies having affinities in the range of 10^8 l/mole. Undue experimentation would be required to produce high affinity antibodies required to

practice methods commensurate with the scope of the claims. Claims 32, 40, 41, 50, 54 and 56 are indefinite, to the extent that they depend from claim 24 in the recitation of an antibody according to claim 1 "or fragment, region" because the meaning is not known. The specification is not enabling for methods of use of pharmaceutical compositions containing undefined antibody fragments. The invention requires compositions which at a minimum, contain fragments which have antigen-binding function.

Claims 32 and 33 are indefinite in the recitation of a pathology mediated by "a" TNF because the particular TNF referred to is not known. The specification is enabling only, for claims drawn to methods for treatment which target TNF-alpha. Claims 40 and 41 are indefinite in the recitation of "malignant pathology" because the meaning is not known. The specification provides no definition. The specification does not enable methods for treating the broadly recited "malignant pathology".

Upon the amendment of claim 33 to depend from claim 48, claims 33, 42, 43, 51, 55 and 57 would be rejected under 35 USC §112, first and second paragraphs for being indefinite to the extent that they depend from claim 48 which depends from claim 6, in the recitation of an antibody "binding with high affinity" because the phrases do not have a defined meaning in the art and the exact values of affinity constants considered to be "high-affinity" antibodies or antibodies "binding with high affinity" are not known. Claims 33, 42, 43, 51, 55 and 57 to the extent that they

depend from claim 48 would be rejected as being are indefinite, to the extent that claim 48 recites "or fragment, region" because the meaning is not known. The specification is not enabling for methods of use of pharmaceutical compositions containing undefined antibody fragments. The invention requires compositions which at a minimum, contain fragments which have antigen-binding function.

Claims 33, 42, 43, 51, 55 and 57 would be rejected as being indefinite in the recitation of a "chimeric" antibody because the term is not one which has a single defined meaning in the art. The specification is enabling only for claims drawn to a chimeric antibody which is characterized in having a human constant region and a mouse variable region. The claims would also be indefinite in the recitation of a chimeric antibody having "at least part of a" constant region and "at least part of a "variable region because the parts of said constant and variable regions referred to are not known. The specification provides no definition. The specification does not teach how to produce chimeric antibodies having less than an entire mouse variable regions which have properties required for therapeutic efficacy in the claimed methods. It is well known that variable region manipulations required to produce engineered antibodies containing less than an entire mouse variable region often significantly affect binding characteristics, frequently resulting in a loss of binding affinity, which property is viewed as being critical to therapeutic

efficacy. The specification provides no direction or guidance to one skilled in the art as to how to produce such antibodies.

27. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, failing to provide an enabling disclosure and failing to present the best mode contemplated by an applicant for carrying out the claimed invention without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of hybridoma cell line c134A which produces the A2 antibody. Because it is not clear that cell lines producing antibodies possessing the exact properties of monoclonal antibody A2 are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the A2 antibody is required in order to identify antibodies having the characteristic of competitively inhibiting binding of Mab A2 which are required to practice the methods of claims 32, 40, 44, 48 and

50, a suitable deposit for patent purposes are required. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of a cell line is an unpredictable event.

Applicant's referral to the deposit of the cell line on pages 17-18 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 met.

Where deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposits will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Where deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding

availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, it is recommended that applicant submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell lines described in the specification as filed are the same as those deposited in the depository, stating that the deposited material is identical to the biological material described in the

specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claims 32, 33, 40-44, 50, 51 and 54-57 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

28. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

The specification is objected to under 35 U.S.C. § 112, first paragraph, and claims 32, 33, 40-44, 50, 51 and 54-57 are rejected under 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 101, as the specification fails to adequately teach how to effectively practice the claimed methods for treating an animal having a pathology mediated by a TNF, said pathology being selected from the group consisting of sepsis syndrome, cachexia, circulatory collapse and shock resulting from acute and chronic bacterial infection, a bacterial infection, a viral infection, a fungal infection, systemic lupus erythematosus, rheumatoid arthritis, and chronic inflammatory pathology and the claimed inventions appear to lack patentable utility.

The provisions of 35 USC § 101 require that the claimed subject matter must be useful in order to be eligible for

patentability. Case law has established that utility must be definite and in currently available form, not based on mere assertion. Brenner v. Manson,383 U.S. 519, 148 USPQ 689 (1966). Where the asserted utility would not be believable on its face to persons skilled in the art in view of the contemporary knowledge in the art at the time the application was filed, as is the case here, the burden is upon the applicant to provide proof of the utility of the claimed inventions. Applicant must provide proof of the utility of the claimed methods which would be convincing to those of skill in the art that the utility of the claimed methods is sufficiently established. See In re Irons, 340 F.2d 924, 144 USPQ 351 (CCPA 1965); Ex parte Krepelka, 231 USPQ 746 (PTO Bd. Pat App. & Inter. 1986); and Ex parte Chwang, 231 USPQ 751 (PTO Bd. Pat. App. & Inter. 1986). Note that when utility is directed to humans, the data must generally be clinical, however, adequate animal data would be acceptable in those instances where one of ordinary skill in the art would accept the correlation to human utility. In order to accept animal data, there must exist an art recognized model for testing purposes.

The specification describes the use of the chimeric A2 monoclonal antibody for treatment of patients suffering from rheumatoid arthritis and the administration of the antibody to a single patient suffering from Crohn's disease, but provides no description or exemplification of the application of the claimed methods for successful treatment of sepsis syndrome, cachexia,

circulatory collapse and shock resulting from acute and chronic bacterial infection, a bacterial infection, a viral infection, a fungal infection, systemic lupus erythematosus, or broadly defined chronic inflammatory pathology. There is no evidence of record which would support a conclusion that the antibodies of the invention would be useful for treatment of the broad spectrum of diseases contemplated, which are highly diverse in their pathologies and underlying mechanisms. The asserted utility or the claimed methods for treatment of the above-listed disorders appears to be based on pure speculation.

Waldmann, in a recent review of the literature pertaining to clinical applications of monoclonal antibodies for diagnosis and therapy of human disease, teaches that effective therapy using monoclonal antibodies has been extremely limited. Harris et al. teach that it is generally recognized by those skilled in the art that there is little future for the use of monoclonal antibodies for in vivo human therapy due to such problems as short halflife, poor recognition of human effector cells and molecules and the human response against mouse proteins (HAMA response). The methods of claims 33, 42, 43, 51, 55 and 57 use chimeric monoclonal antibodies. With respect to chimeric monoclonal antibodies, Harris et al. teach that the HAMA response is greatly reduced. However, the anti-idiotypic HAMA response elicited by chimeric antibodies is viewed as rendering repeated dosing ineffective. Certain embodiments of the claims relate to methods for treatment of septic

shock using a TNF-specific monoclonal antibody which neutralizes the biological activity of human TNF. Septic shock is a complex and incompletely understood syndrome which is well known to be refractory to effective therapy. Parrillo reviews the pathogenic mechanism of septic shock and discusses potential strategies for treatment of septic shock. The reference indicates that the pathogenic mechanisms leading to morbidity and mortality in septic shock are incompletely understood. Parrillo discusses the potential utility of inhibitors of mediators of septic shock for treatment, stating on page 1476, col. 2 that "A word of caution is warranted regarding the use of inhibitors of the mediators of septic shock. The pathogenetic mechanisms of septic shock are complex and interdependent, and many of them represent the body's compensatory response to sepsis and therefore have salutary effects." It is clear from the discussion of Parrillo, that the utility of inhibitors of mediators in the treatment of septic shock is at the present time under development and that such therapies are not recognized as being established and in currently available form. Pennington reviews the current state of the art relating to therapy of sepsis using monoclonal antibodies which neutralize TNF. Pennington teaches that it has not yet been determined in the art whether neutralizing potentially harmful cytokines, such as TNF, in the septic patient can improve outcome (see e.g. page 482). Verhoef et al. review the state of the art relating to the use of monoclonal antibodies for treatment of bacterial infection and

indicate that further research is required before monoclonal antibodies will be considered to be applicable for routine use. In view of the lack of established utility of antibodies specific for cytokines which are mediators of sepsis, those of skill in the art would not find the asserted utility of the claimed methods for treating septic shock, believable on its face in the absence of convincing experimental evidence which establishes that the claimed methods are effective. A similar rationale can be applied to the numerous other diseases contemplated for treatment of the claimed methods. In view of the contemporary knowledge in the art of the general lack of successful application of monoclonal antibody-based therapy methods for the treatment of human diseases, those of skill in the art would not view applicant's assertions that the claimed antibody-based methods are useful for treatment of sepsis syndrome, cachexia, circulatory collapse and shock resulting from acute and chronic bacterial infection, a bacterial infection, a viral infection, a fungal infection, systemic lupus erythematosus, and chronic inflammatory pathology, in the absence of convincing experimental evidence establishing the utility of the claimed invention.

With respect to the efficacy of the claimed methods for treating rheumatoid arthritis, it is unclear from the limited data reported in the specification, that the methods of the invention are effective for treatment of rheumatoid arthritis. It appears from Tables 4-5 on page 90, that the patients in the trial all

received concomitant therapy with anti-rheumatic drugs and chimeric A2. Therefore, it is not clear whether the improvements in patient condition reported in the specification are the result of antibody therapy. It is expected that there will be a need for repeated administration of anti-TNF antibodies in order to practice the claimed methods. It is unclear whether efficacy of antibodies would be limited by HAMA response upon probable readministration of the antibodies. The efficacy of murine antibodies in the claimed methods has not been demonstrated. As discussed above, it is known in the art that murine antibodies have characteristics which may severely limit their use in human therapy. The probable need for readministration of such therapeutic modalities in disorders treated by the claimed methods increases these risks. The limitations of murine antibodies for use in the claimed methods are acknowledged in applicant's specification, for example, at pages 7 and 49, which teaches that murine monoclonal antibodies may have properties which are undesirable for human therapeutic use, such as short circulating half life and immunogenicity which decrease the effectiveness of continued administration and can render treatment ineffective.

The record does not contain evidence of the efficacy of the claimed methods which is commensurate with the scope of the claims. The exemplification of the successful use of a single antibody in a method for the treatment of a single disease would be enabling only for a claim drawn to a method for treatment of the exemplified

disease using the exemplified antibody. The instant claims require the use of a pharmaceutical composition containing a high affinity mouse monoclonal antibody to human TNF-alpha which competitively inhibits the binding of antibody A2 and binds to a neutralizing epitope of TNF-alpha or a pharmaceutical composition containing a chimeric antibody binding with high affinity to a neutralizing epitope of TNF-alpha comprising at least part of a variable region having specificity for human TNF-alpha. The efficacy of antibody-based treatment methods is significantly affected by many different antibody variables. There is no evidence of record which establishes that the ability to effectively mediate therapy of pathologies in which TNF is a mediator, is a general property of chimeric antibodies which bind to a neutralizing epitope of TNF or of high affinity antibodies which competitively inhibit the A2 Mab. The teachings of applicant's specification would suggest that this will not be the case. See for example, page 83 of the specification wherein three anti-TNF antibodies designated TNF-1 to 3 which are characterized as being of comparable binding affinity to TNF as compared with the murine and chimeric antibodies of the invention, are described as being significantly less potent in neutralization than the antibodies of the invention.

The specification contemplates that antibodies according to the invention, which are used in the claimed methods, include human antibodies. The difficulties associated with obtaining stable cell lines secreting human antibodies having a particular desired

binding specificity are well established in the art. The successful production of cell lines secreting human monoclonal antibodies is dependent upon the availability of a source of human immune lymphocytes producing an antibody of the desired specificity. Applicant has provided no evidence of the availability of sources of human lymphocytes producing high-affinity antibodies specific neutralizing epitopes of human TNF-alpha or which are capable of competitively inhibiting binding of monoclonal antibody A2 to TNF and which have having properties required for successful therapeutic use. Given the unpredictability of isolating lymphocytes producing antibodies having the properties described above, together with the lack of a specific teaching of a source of such lymphocytes, which would be required for the production of the claimed antibodies, it appears that undue experimentation would be required of one of skill in the art to practice the claimed invention using the teaching of the written specification alone.

28. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of

this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

29. Claims 32, 40, 41, 50, 54, and 56 are rejected under 35 U.S.C. § 103 as being unpatentable over Tracey et al. (Nature 330) or DiGiovine et al. (Ann. Rheum. Dis. 47) or Herve et al (Lymphoma Res. 9) or Piguet et al. (J. Exp. Med. 166) or Akama et al. (BBRC 168) in view of Moller et al. or WO9102078.

Tracey et al. teach a method for prevention of septic shock during bacterial infection by administration of anti-TNF-alpha antibodies to baboons. Tracey conclude that TNF-alpha is a mediator of fatal bacteremic shock and suggest that antibodies against TNF-alpha (cachectin) offer a potential therapy of infection. (See for example, the abstract).

DiGiovine et al. teach that elevated levels of TNF were detected in synovial fluids from patients with different rheumatoid diseases and suggest that TNF contributes to the pathogenesis of joint damage in chronic rheumatoid diseases.

Akama et al. teach that TNF-alpha appears to play an important role in the development of inflammation, such as rheumatoid arthritis by enhancing arachidonic acid metabolism of polymorphonuclear cells and that an anti-TNF-alpha antibody inhibited stimulation by LPS-stimulated mononuclear cell supernatants, of arachidonic acid metabolism as measured by increased production of prostaglandin E2 by polymorphonuclear

cells.

Herve et al. teach that TNF-alpha was recognized to play an important role in the pathogenesis of GvHD in mice and humans and describe the administration of an anti-TNF-alpha antibody for prevention of GvHD.

Piguet et al. teach that TNF-alpha was believed to play a role in the etiology of skin and gut lesions of the acute phase of graft-versus host disease and describe the prevention of lesions of the acute phase of GvHD in mice by administration of rabbit anti-TNF antibodies. The references do not teach that the antibodies used have the characteristics of those used in the claimed methods.

Moller et al., teach monoclonal antibody M195 which appears to be the same as the antibody contained in the pharmaceutical composition used in the claimed methods.

WO9102078 teaches high affinity TNF-specific monoclonal antibodies which bind to neutralizing epitopes. Certain of these antibodies bind to epitopes located within synthetic peptides corresponding to TNF-alpha, which contain an epitope recognized by the A2 antibody. According to the teaching of the specification the A2 antibody binds to synthetic peptides comprising residues 87-108 and 59-80. According to the teaching on page 33 of the reference, Mab 1 binds to a peptide consisting of residues 58-65, Mab 11 binds to a peptide consisting of residues 49-98, Mab 42 binds to a peptide consisting of residues 49-96, Mab 54 binds to a peptide consisting of residues 56-79, etc. Results of competitive

binding assays using the referenced antibodies are shown in Fig 9. The antibodies are shown to inhibit biological activities of TNF-alpha according to the teaching in Table 2, page 22. At least some of the referenced antibodies would be expected to competitively inhibit binding of Mab A2 of the instant invention to TNF-alpha.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of the cited prior art and to use high affinity TNF-neutralizing monoclonal antibodies such as those taught by Moller et al., and WO9102078 in methods for treatment of humans or other animals suffering from pathologies in which TNF-alpha was recognized to be a mediator, such as bacterial sepsis, inflammatory diseases such as rheumatoid arthritis and graft-versus-host disease as disclosed by the primary references. One of ordinary skill in the art would have been motivated to do so in view of the expectation by those of ordinary skill in the art that antibodies capable of inhibiting TNF-alpha biological activity had potential utility for treatment of various pathologies in which TNF was recognized to be a mediator. It would have been well within the level of ordinary skill in the art to determine suitable dosages of anti-TNF antibodies for administration in the methods suggested by the combined teachings of the prior art.

30. Claims 33, 42, 43, 51 and 57 are rejected under 35 U.S.C. § 103 as being unpatentable over Tracey et al. (Nature 330) or DiGiovine et al. (Ann. Rheum. Dis. 47) or Herve et al (Lymphoma

Res. 9) or Piguet et al. (J. Exp. Med. 166) or Akama et al. (BBRC 168) in view of Bringman et al. or Moller et al. or WO9102078 or and further in view of Morrison.

Tracey et al. teach a method for prevention of septic shock during bacterial infection by administration of anti-TNF-alpha antibodies to baboons. Tracey conclude that TNF-alpha is a mediator of fatal bacteremic shock and suggest that antibodies against TNF-alpha (cachectin) offer a potential therapy of infection. (See for example, the abstract).

DiGiovine et al. teach that elevated levels of TNF were detected in synovial fluids from patients with different rheumatoid diseases and suggest that TNF contributes to the pathogenesis of joint damage in chronic rheumatoid diseases.

Akama et al. teach that TNF-alpha appears to play an important role in the development of inflammation, such as rheumatoid arthritis by enhancing arachidonic acid metabolism of polymorphonuclear cells and that an anti-TNF-alpha antibody inhibited stimulation by LPS-stimulated mononuclear cell supernatants, of arachidonic acid metabolism as measured by increased production of prostaglandin E2 by polymorphonuclear cells.

Herve et al. teach that TNF-alpha was recognized to play an important role in the pathogenesis of GvHD in mice and humans and describe the administration of an anti-TNF-alpha antibody for prevention of GvHD.

Piguet et al. teach that TNF-alpha was believed to play a role in the etiology of skin and gut lesions of the acute phase of graft-versus host disease and describe the prevention of lesions of the acute phase of GvHD in mice by administration of rabbit anti-TNF antibodies.

Bringman et al., Moller et al., and WO9102078 each teach high affinity TNF-specific monoclonal antibodies which bind to neutralizing epitopes.

Morrison teaches methods for the production of chimeric antibodies and that chimeric antibodies were recognized to be superior to murine antibodies for in vivo therapy in humans.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of the cited prior art and to use high affinity TNF-neutralizing monoclonal antibodies such as those taught by Bringman et al., Moller et al., and WO9102078 in methods for treatment of humans or other animals suffering from pathologies in which TNF-alpha was recognized to be a mediator, such as bacterial sepsis, inflammatory diseases such as rheumatoid arthritis and graft-versus-host disease as disclosed by the primary references. It would have been obvious to produce chimeric antibodies having the variable regions of the prior art antibodies for use in the claimed methods. One of ordinary skill in the art would have been motivated to do so in view of the teaching of Morrison of the recognized advantages of chimeric antibodies for

use in <u>in vivo</u> therapy of diseases in humans.

It would have been well within the level of ordinary skill in the art to determine suitable dosages of anti-TNF antibodies for administration in the methods suggested by the combined teachings of the prior art.

31. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

32. Claims 32 and 56 are rejected under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Moller et al.

Moller et al. teach a method for protection of mice treated with Lethal doses of TNF-alpha by administering monoclonal antibody M195 (see page 168) M195 is functionally similar to the A2 antibody as characterized in the specification, in exhibiting high affinity binding to TNF-alpha, neutralizing TNF-alpha but not TNF beta (see p. 164 Table 2) binding to human and chimpanzee TNF but not TNF from baboon, rhesus monkey or cynomolgus monkey (p. 164 col. 1). In view of those similarities, the A2 and M195 antibodies appear to have the same or similar epitope binding specificities. Accordingly, the ability to competitively inhibit binding of A2 is

deemed to necessarily be an inherent property of the A2 antibody, in the absence of evidence to the contrary, and the referenced method appears to be the same as that claimed.

Even if the claimed method differs slightly from the referenced method, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to follow the teachings of the reference and to produce additional high-affinity antibodies having specificity for neutralizing epitopes of TNF-alpha and to use said antibodies in methods for treatment of pathologies in which TNF-alpha is a mediator. One of ordinary skill would have been motivated to do so in view of the teaching of Moller et al.

33. The first paragraph of the specification states that the instant application is a continuation of each of applications 07/943,852, 07/853,606 and 07/670,827. While this application repeats a substantial portion of prior application Serial Nos. 07/943,852, 07/853,606 and 07/670,827, it adds claims and additional disclosure not presented in the prior applications. Since this application names an inventor or inventors names in the prior application, it constitutes a continuation-in-part of the prior application. Attention is directed to 35 U.S.C. 120 and 37 C.F.R. 1.78. Additionally, it is pointed out that application 07/943,852 is a continuation-in-part of application Serial No. 07/853,606 which is a continuation-in-part of application 07/670,827. Correction of the continuing data in the first

paragraph of the specification is requested.

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paula Hutzell whose telephone number is (703) 308-4310.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Hutzell/lg
October 26, 1993

PAULA K. HUTZELL
PATENT EXAMINER
GROUP 1800